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March 15, 2004

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

INVENTOR(S)		
Given Name (first and middle (if any))	Family Name or Surname	Residence (City and either State or Foreign Country)
Gregory N.	Beatch	Vancouver, Canada

☐ *Additional inventors are being named on the ____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (280 characters max)

ANTIARRHYTHMIC DRUGS

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 10
☒ Drawing(s) *Number of Sheets* 7
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☐ Applicant claims small entity status. See 37 CFR 1.27.
☐ A check or money order is enclosed to cover the filing fees
☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number 06-0713
☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE AMOUNT ($): $160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE

Date 02 May 03

TYPED or PRINTED NAME Brian G. Kingwell

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Docket Number: 82836-15

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C.

P19SMALL/REV05

ANTIARRHYTHMIC DRUGS

FIELD OF THE INVENTION

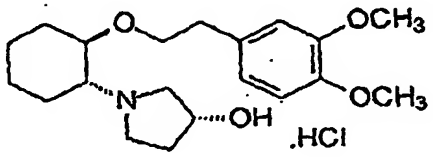
The invention is in the field of therapeutic compositions.

SUMMARY OF THE INVENTION

RSD1235 is a new chemical entity useful for treating arrhythmia, particularly as an agent for the acute conversion and maintenance of sinus rhythm in patients with atrial fibrillation (AF). Intravenously administered RSD1235 has recently been shown to be safe and effective for acute conversion of AF in patients (n=56) with AF episodes (3h<AF<72h) of new or recurrent origin (the CRAFT Study). The current Phase I was a prospective, randomized, placebo-controlled, double-blind, ascending dose bioavailability study of an orally administered aqueous formulation of RSD1235 in healthy volunteers. Pharmacokinetic assessment and safety monitoring endpoints were evaluated with first patient dosed on November 12, 2002. Dosing was completed on December 10, 2002. All doses were administered as a single oral dosing solution.

Compound: RSD1235

Chemical name:(1*R*, 2*R*)-2-[(3*R*)-hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)cyclohexane monohydrochloride



Molecular formula: $C_{20}H_{31}NO_4.HCl$

FW: 385.93

The following report represents a summary of the unaudited data. All safety analyses, including classification of adverse events, were analyzed (by Pharma Bio-Research B.V., Zuidlaren, Netherlands) blinded to treatment group, prior to breaking the study randomization code.

This Phase I prospective, randomized, placebo-controlled, double-blind, ascending dose study was conducted to assess safety and oral absorption of RSD1235 in healthy volunteers. Safety and tolerance were monitored through 12-lead ECG, Holter and telemetry recordings and monitoring of clinical observations, vital signs, clinical chemistries and haematology. The pharmacokinetics was assessed through measurement of RSD1235 levels in both urine and plasma.

The C_{max} in fasted volunteers was 1.8 ± 0.4 µg/ml after the 5 mg/kg p.o. dose and 1.9 ± 0.5 µg/ml after the 7.5 mg/kg p.o. dose. In fed volunteers, the C_{max} was 1.3 ± 0.7 µg/ml after the 5 mg/kg p.o. dose. There were no statistically significant differences in C_{max}, time to maximum plasma levels (T_{max}), or bioavailability (F%) between the groups. The oral bioavailability in the three dosing groups were found to be 71 ± 21% (mean ± s.d.), 69 ± 50% and 58 ± 19%, for 5 mg/kg fasted, 5 m/kg fed and 7.5 mg/kg fasted respectively, indicating that RSD1235 is rapidly and extensively absorbed after oral administration. The plasma levels achieved were well within the therapeutic range (median plasma level at ED_{60} = 1.3 µg/ml) as observed in the recently completed intravenous CRAFT trial (Cardiome Recent onset Atrial Fibrillation Trial). The results are supportive of future development of this agent for the chronic management of AF patients.

RSD1235 was found to be well-tolerated in oral doses of up to 7.5 mg/kg. Vital signs, BP and lab results remained normal in all subjects. There were no changes in QT or any ECG intervals observed in any of the dosing groups. No serious adverse events reported. Of the total 23 adverse events (AEs) reported, five AEs were reported in subjects receiving placebo, and 18 AEs reported in subjects receiving active drug. Of the 18 AEs reported in subjects receiving active drug, only five events were identified as "possibly" related to study drugs. All of the adverse events were classified as "mild", except for a "moderate" AE that occurred at admission and was deemed "not related" to study drug.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Vital Signs in "fasted" Volunteers RSD1235 (5 mg/kg p.o.)

Figure 2. Vital Signs in "fed" Volunteers RSD1235 (5 mg/kg p.o.)

Figure 3. Vital Signs in "fasted" Volunteers RSD1235 (7.5 mg/kg p.o.)

Figure 4. ECG Intervals in "fasted" Volunteers RSD1235 (5 mg/kg p.o.).

Figure 5. ECG intervals in "fed" volunteers RSD1235 (5 mg/kg p.o.).

Figure 6. ECG intervals in "fasted" volunteers RSD1235 (7.5 mg/kg p.o.).

Figure 7. ECG intervals in placebo volunteers.

DETAILED DESCRIPTION OF THE INVENTION

OVERVIEW

Study Objectives

1. To determine the oral absorption and bioavailability of RSD1235 (relative to intravenous administration in a previous study, MDS Pharma Services, Project 26450, August 2001) in normal healthy human volunteers.

2. To determine the safety and tolerability of RSD1235 given as a single oral dose of 5.0 or 7.5 mg/kg in fasted and fed (5.0 mg/kg only) normal healthy human volunteers.

Investigators and Study Administrative Structure

The study was performed under the direction of Corine M. Hofland-Hulzinga, M.D., Principal Investigator, at Pharma Bio-Research Group BV, Zuidlaren, The Netherlands.

The clinical laboratory tests required by the protocol were performed at the Pharma Bio-Research Clinical Laboratory.

Sample analysis for RSD1235 was performed at MDS Pharma Analytical Services, Montréal, Quebec, Canada.

Medical monitoring of the study was conducted by Garth Dickinson, MD, FRCPC, Medical Consultant, Ottawa, Ontario, Canada and overall monitoring was conducted by Joanne Brown, Cardiome Pharma Corp.

Study Design, Analysis and Dosing Schedule

The Phase I Oral RSD1235 study was a prospective, randomized, placebo-controlled, double-blind ascending single-dose dose assessment of the oral bioavailability of RSD1235. Dose ranging covered two doses (5.0 and 7.5 mg/kg) and involved 24 volunteers. The study was conducted in 3 dosing blocks. After completion of each dosing block and assessment of clinically significant findings, the blind was broken and RSD1235 plasma levels were analyzed prior to continuation of the next dosing block. Interim safety review meetings were held to review all of the available data after dosing blocks 1 and 2.

All subjects were admitted to the study facility the evening before dosing and were monitored for 24-hours in the facility post-dose with a 1-week +/- 3 days follow-up visit. Volunteers received a single dose (150 ml solution) of RSD1235 or placebo given on one occasion. The first 8 subjects were randomized to receive either placebo (n=2) or to receive a single oral administration of 5.0 mg/kg oral dose (n=6). The first 8 subjects were fasted from midnight prior to dosing until four hours post-dose. The second group of subjects were assessed at the same dose (5 mg/kg) with fed subjects (n=6) and placebo (n=2). A standard breakfast was administered concomitant with dosing. The third group of 8 subjects were randomised to receive either placebo (n=2) or to receive a single oral administration of 7.5 mg/kg (n=6). These subjects were fasted from midnight prior to dosing until four hours post-dose.

Table 1. Dosing Schedule

	Placebo	5.0 mg/kg	7.5 mg/kg
Block 1 Subjects 01-08	2 (Fasted)	6 (Fasted)	
Block 2 Subjects 09-16	2 (Fed)	6 (Fed)	
Block 3 Subjects 17-24	2 (Fasted)		6 (Fasted)

Study Population

Inclusion & Exclusion Criteria

The subjects for this study were normal, healthy males and females as defined by the inclusion and exclusion criteria described below:

Inclusion Criteria

a) Females and males aged 18 between 60 years. Females must be non-pregnant and surgically sterile or free of menses for more than two years. If free of menses females must be using an effective form of birth control during the study (from pre-screening) until three months after the follow-up visit. Methods of birth control considered to be effective would include hormonal contraception (the pill), an intrauterine device (IUD), condoms in combination with a spermicidal cream, total abstinence or sterilisation. Males will be advised to refrain from unprotected sexual intercourse (i.e., without adequate contraceptive method) until three months after the follow-up screening).

b) No clinically important abnormal physical findings at the screening examination.

c) Normal ECG.

d) Body weight between 45 to 95 kg and a body mass index of 18-27 kg/m^2.

e) Able to communicate well with the investigator and to comply with the requirements of the entire study.

f) Provision of written informed consent to participate as shown by a signature on the volunteer consent form.

Exclusion Criteria

a) 90 mmHg > systolic blood pressure > 160 mmHg, or, 65 mm Hg > diastolic pressure > 95 mmHg. These will be measured 3 times after sitting for 3 minutes and averaged to determine a baseline BP.

b) 50 bpm ≥ pulse rate ≥ 90 bpm.

c) PR > 0.21 sec, QRS > 0.11 sec, QT_cB > 0. 430 sec for men and QT_cB > 0.450 sec for women.

d) Participation in any other investigational drug study within 60 days preceding the start of the study, or participation in more than 3 other drug studies (for men) / more than 2 other drug studies (for women) in the past 10 months.

e) Administration of prescription or over-the-counter medication during the period 0 to 5 days before entry to the study including aspirin. (Exceptions to this criterion include the use of hormone replacement therapy or oral contraceptives by female subjects.)

f) Administration of antacids, gastric reflux, anti-ulcer or gastrointestinal pro-kinetic medications in the period of 0 to 30 days before entry to the study unless agreed upon by Sponsor and Investigator.

g) Existence of any surgical or medical condition which, in the judgement of the clinical investigator, might interfere with the absorption, distribution, metabolism or excretion of the drug.

h) Donation of blood within 60 days preceding the start of the study, or, donation of more than 1.5 liters of blood (for men) / more than 1.0 liters of blood (for women) in the past 10 months. (The exception to this criterion is, blood sampling for screening, admission and baseline tests for this study is permitted.)

i) Loss of greater than 250 ml of blood within 60 days preceding the start of the study.

j) Known serious adverse reaction or hypersensitivity to any drug.

k) Inability to communicate or co-operate with the investigator because of a language problem, poor mental development or impaired cerebral function.

l) Positive drug screen, positive Ab to HIV, HCV, and positive Ag to HBV

m) History of drug or alcohol abuse.

n) Abnormal screening test results (clinical chemistry, hematology or urinalysis).

o) Family history of QT abnormalities or congenital QT syndrome.

p) Any herbal or alternate medicines during the period 0 to 5 days before entry to the study.

q) Frequent use of antacids

r) History of gastro-intestinal or cardiovascular problems.

s) Any other condition that, in the opinion of the clinical investigator, would make it unwise to enter the subject into the study.

Restrictions

No alcohol, caffeine or smoking were permitted from admission to the study facility to discharge. No herbal remedies, medicines or alternative medicines were permitted from admission to the study facility to discharge with the exception of aspirin/paracetamol which was permitted from 4 h post-dose onwards.

Criteria for Stopping Dosing

Dosing was to be terminated if any volunteer that exhibited any significant clinical signs (e.g. tremors) or if the following limits were reached:

- PR > 0.24 s
- QTcB > 0.500s
- Pulse Rate < 40 bpm
- Systolic BP <80 mm Hg (confirmed by three measurements over three minutes)
- Evidence of bundle branch block or other serious conduction disturbance.

Subject Demographics

The subject population included men (63%) and women in the age range of 18 – 60 years. Subject body weight ranged from 59.1 to 89.3 kg. Subjects meeting entry criteria and signing informed consent forms were enrolled in the study. Each subject was assessed clinically pre-dose and underwent clinical and pharmacokinetic evaluation during and after dosing. Each subject enrolled in the study was characterized for cytochrome P450 2D6 expression by genotyping using a blood sample. Table 2 details the demographic characteristics of the 24 subjects.

Table 2. Subject Demographics

Group	Subject	Gender *	Age (y)	Weight (kg)	Height (cm)	BMI (kg/m^2)
1	01 JH	F	59	71.1	167	25.5
1	02 DB	F	54	74.6	166	27.1
1	03 MB	F	56	59.1	149	26.6
1	04 RR	M	58	77.3	173	25.8
1	05 DF	M	59	77.7	182	23.5
1	06 BP	M	59	83.0	180	25.6
1	07 EM	M	20	87.2	190	24.2
1	08 VS	F	60	62.6	156	25.7
2	09 EJ	M	58	73.8	173	24.7
2	10 AH	F	58	67.4	164	25.1
2	11 IH	M	51	82.2	176	26.5
2	12 JB	F	59	70.1	166	25.4
2	13 GK	F	47	70.8	176	22.9
2	14 CB	M	59	89.3	184	26.4
2	15 DJ	M	23	87.0	181	26.6
2	16 HL	M	18	67.1	191	18.4
3	17 MH	M	20	66.3	185	19.4
3	18 FV	M	21	73.3	181	22.4
3	19 RV	M	52	85.5	176	27.6
3	20 RP	M	30	75.5	179	23.6
3	21 MR	M	25	79.8	181	24.4
3	22 JW	F	53	79.4	170	27.5
3	23 KR	M	19	69.5	183	20.8
3	24 KS	F	53	59.3	162	22.6
Minimum			18	59.1	149	
Maximum			60	89.3	191	
Mean			45	74.5	175	
s.d.			16.8	8.6	10.5	

* M = male
F = female

Study Procedures and Assessments

- The study drug was administered in a volume of 150 mL by oral administration. If drug/placebo was administered to fed subjects, then drug/placebo was administered to subjects with a standard breakfast.
- Subjects remained sitting during drug administration and it was encouraged that they remained sitting for approximately 4 hours post-dose.
- Telemetry monitoring was conducted from baseline until at least 4 hours post-dose.
- Vital signs measurements including pulse rate, respiration rate, blood pressure and oxygen saturation were taken at the following timepoints: screening; admission; pre-dose; immediately following dosing; 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours after drug/placebo administration; at follow-up visit; and in the event of an SAE (none occurred).
- 12-lead ECGs were recorded at the following timepoints: screening; admission; pre-dose; immediately following dosing; 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours after drug/placebo administration; at follow-up visit; and in the event of an SAE (none occurred). ECG's were interpreted by a board-certified cardiologist selected by the Sponsor. Baseline and screening 12-lead ECGs were recorded three times consecutively after subject had been sitting for 10 minutes. The ECG recording with the median of the three QTcB interval measurements was used as the ECG for that timepoint.
- Blood (5 mL) for pharmacokinetic analysis were drawn at the following timepoints via venipuncture or sampling canula into lithium heparin tubes: pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours after drug/placebo administration and in the event of an SAE (none occurred). Pharmacokinetic (PK) parameters for each subject were calculated using WinNonlin (Pharsight Corp., Palo Alto, California, USA). A non-compartmental model was used to calculate parameter estimates. The oral bioavailability of RSD1235 was calculated using the area under the curves (AUCs) after oral administration compared to the AUCs obtained after iv administration in a previously completed study (Phase I trial report).
- Urine was collected each time the subject voided. After dosing specimens were collected over the periods: 0-4 hours, 4-8 hours and 8 hours - discharge.
- Clinical chemistry, hematology, and urinalysis at screening, admission, at 1 hour post-dose and at discharge.
- Holter monitoring continued for up to 24 hours post-dose. Holter monitors were read at a central reading centre.
- The nature of any adverse event, its time of onset, its duration and severity, action taken, if any, and the investigator's opinion as to whether it was related to the test drug was recorded on the AE Form. Duration of the follow up of an adverse event was until recovery from the event was evident, or until the event was judged medically stable or permanent. Subjects were monitored in the study facility until all adverse events resolved

RESULTS

Safety Assessment

5.1.1 Adverse Events & Laboratory Evaluations

Throughout the study the subjects were closely monitored. They were queried about the occurrence of subjective complaints (adverse events) daily using non-leading questions. The nature and time of occurrence of the reported or observed adverse events are tabulated in Table 3. The relationship between the adverse events and the study

medication is indicated as, 'not related', 'unlikely', possible', "probable' or 'definitely'. Neither serious nor severe adverse events were observed.

Table 3. Adverse Events

Block 1 (5.0 mg/kg or placebo in fasted state)						
Subject	Medication time (h:min)	Adverse event	Onset day (time)	End day (time)	Intensity	Relationship
04 (P)	08:42	Rhinitis	-5 (NR)	ongoing	mild	not related
05 (D)	08:46	Headache	-1 (18:10)	1 (07:00)	mild	not related
		loose stools	1 (10:15)	1 (10:45)	mild	possibly
07 (D)	08:54	taste bitter	1 (08:55)	1 (18:30)	mild	possibly
08 (P)	08:58	fell asleep	1 (10:20)	1 (10:30)	mild	not related
		fell asleep	1 (15:00)	1 (15:20)	mild	not related
		incr. Defecation frequency	-1 (NR)	1 (17:00)	mild	not related

Block 2 (5.0 mg/kg or placebo in fed state)						
Subject	Medication time (h:min)	Adverse event	Onset day (time)	End day (time)	Intensity	Relationship
12 (D)	08:42	Tiredness	1 (10:00)	1 (16:00)	mild	not related
14 (D)	08:50	pain back	1 (07:00)	ongoing	mild	not related
16 (D)	10:02	pain canula site	-1 (20:15)	1 (21:00)	mild	not related
		collapse	-1 (20:38)	-1(20:40)	moderate	not related

Block 3 (7.5 mg/kg or placebo in fasted state)						
Subject	Medication time (h:min)	Adverse event	Onset day (time)	End day (time)	Intensity	Relationship
17 (D)	08:30	Headache	1 (16:30)	1 (16 :31)	mild	not related
21 (P)	08:46	Tiredness	1 (06:30)	1 (13 :00)	mild	not related
22 (D)	08:50	dry mouth	2 (07:00)	-	mild	not related
		dry nose	2 (07:00)	-	mild	not related
		epistaxis	2 (07:00)	2 (07:01)	mild	not related
23 (D)	08:54	Tiredness	1 (09:45)		mild	not related
		Paresthesia r. hand	1 (12:31)	1 (12 :31)	mild	possibly
		vision disorder	1 (13:00)	2 (08 :00)	mild	possibly
		paresthesia r. hand	1 (18 :15)	1 (18 :15)	mild	possibly
24 (D)	08:58	Headache	-1 (23:00)	2 (05 :30)	mild	not related
		Sleepiness	1 (10 :00)	2 (05 :30)	mild	not related
		SVT (7 beats)	2 (01 :07)	2 (01 :07)	mild	unlikely

Note: (D) = drug, (P) = placebo treatment

Dosing Block 1: RSD1235 (5 mg/kg) or Placebo in "Fasted" Volunteers

Seven adverse events were reported by four out of eight "fasted" subjects. Of these four subjects, two had received study drug. All of the observed experiences were of a mild intensity. Only two of the adverse events were identified as possibly related to the study medication: loose stools (1 hr, 29 mins post-dosing) in subject 05 and bitter taste (1 mins post-dosing) in subject 07

In the clinical laboratory test results no clinically relevant changes from the baseline were observed.

Dosing Block 2: RSD1235 (5 mg/kg) or Placebo in "Fed" Volunteers

Four adverse events were reported by three out of eight "fed" volunteers in dosing block 2. All three of these subjects had received study drug. All of the adverse events were identified as not related to the study medication. Three of the observed experiences were of a mild intensity, the collapse of subject 16 HL was of moderate intensity and occurred the day prior to dosing.

In the clinical laboratory test results no clinically relevant changes from the baseline were observed.

Dosing Block 3: RSD1235 (7.5 mg/kg) or Placebo in "Fasted" Volunteers

Twelve adverse events were reported by five of eight "fasted" volunteers in dosing block 3. Of these five subjects, four had received study drug. All of the observed experiences were of mild intensity. Three of the adverse events (all in one volunteer) were considered possibly related to the study medication. These consisted of two transient episodes of paraesthesia in the right (3 hrs, 37 mins and 9 hrs, 21 mins post-dosing) and a vision disturbance (4 hrs, 6 mins post-dosing).

In the clinical laboratory test results no clinically relevant changes from the baseline were observed.

Vital Signs

Vital signs were measured at regular intervals. Blood pressure, heart rate, O_2-saturation and oral body temperature showed no changes of clinical relevance in any of the dosing groups. The systolic blood pressure, diastolic blood pressure and pulse rate are shown for the 5 mg/kg dose in fasted subjects, the 5 mg/kg dose in fed subjects, the 7.5 mg/kg dose in fasted subjects in Figures 1, 2 and 3 respectively.

12-lead ECG and Holter Reports

12-lead ECG recordings obtained before and during the study for all dosing groups, showed no changes of clinical relevance. Figures 4, 5, 6 and 7 indicate 12-lead ECG interval recordings measured by the board-certified cardiologist at each scheduled timepoint for; the 5 mg/kg dose in fasted subjects, the 5 mg/kg dose in fed subjects, the 7.5 mg/kg dose in fasted subjects and subjects receiving placebo, respectively. No clinically relevant changes in any of the parameters were observed (QTcB, QT, JT, PR, QRS, HR). Telemetric monitoring of all subjects, during the first 4 hours after the single dose of the study period, showed no clinically relevant abnormalities. During the holter monitoring recorded from admission (-1) until discharge (day 2), no relevant changes from the baseline were observed.

Although various embodiments of the invention are disclosed herein, many adaptations and modifications may be made within the scope of the invention in accordance with the common general knowledge of those skilled in this art. Such modifications include the substitution of known equivalents for any aspect of the invention in order to achieve the same result in substantially the same way. Numeric ranges are inclusive of the numbers defining the range. The word "comprising" is used herein as an

open-ended term, substantially equivalent to the phrase "including, but not limited to", and the word "comprises" has a corresponding meaning. As used herein, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a thing" includes more than one such thing. Citation of references herein is not an admission that such references are prior art to the present invention. All publications, including but not limited to patents and patent applications, cited in this specification are incorporated herein by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein and as though fully set forth herein. The invention includes all embodiments and variations substantially as hereinbefore described and with reference to the examples and drawings.

ABSTRACT

The invention provides therapeutic compositions comprising (1*R*, 2*R*)-2-[(3*R*)-hydroxypyrrolidinyl]-1-(3,4- dimethoxyphenethoxy)cyclohexane monohydrochloride, useful for treating arrhythmia, particularly as an agent for the acute conversion and maintenance of sinus rhythm in patients with atrial fibrillation.

Figure 1

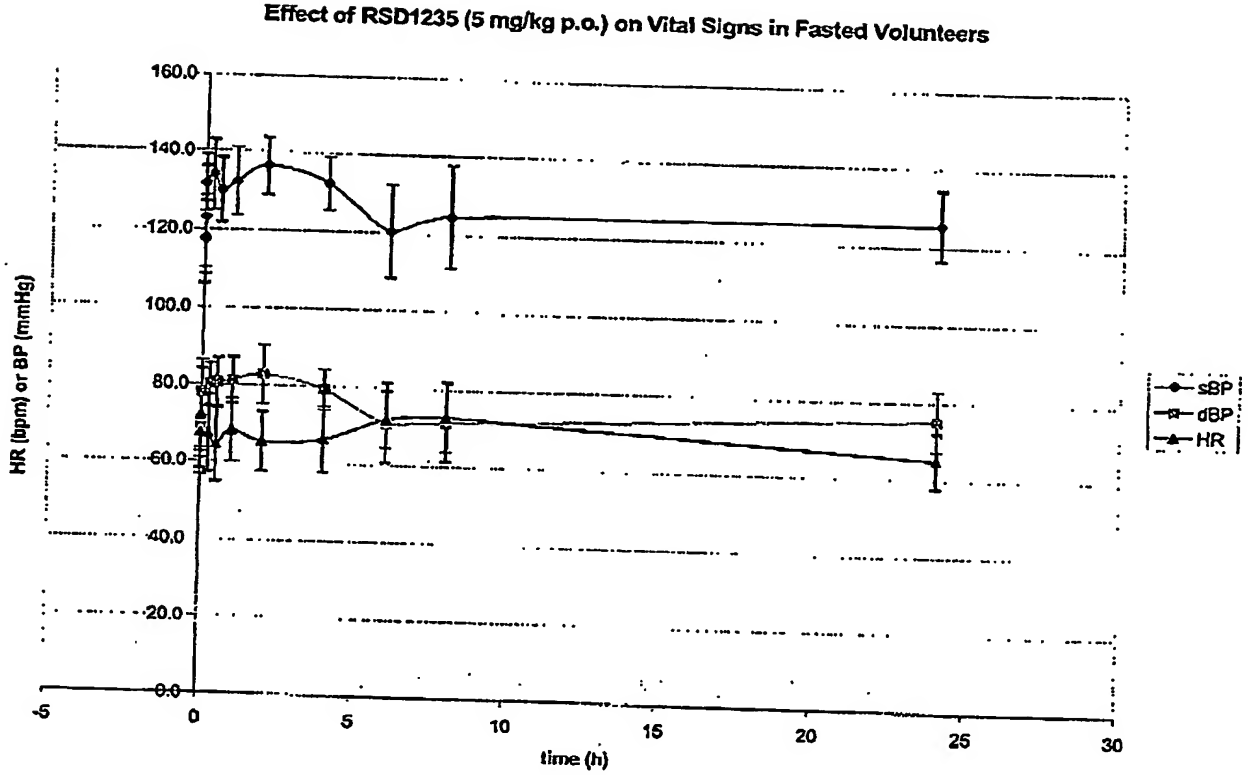

Effect of RSD1235 (5 mg/kg p.o.) on Vital Signs in Fasted Volunteers
HR (bpm) or BP (mmHg)
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
-5
0
5
10
15
20
25
30
time (h)
sBP
dBP
HR

Figure 2

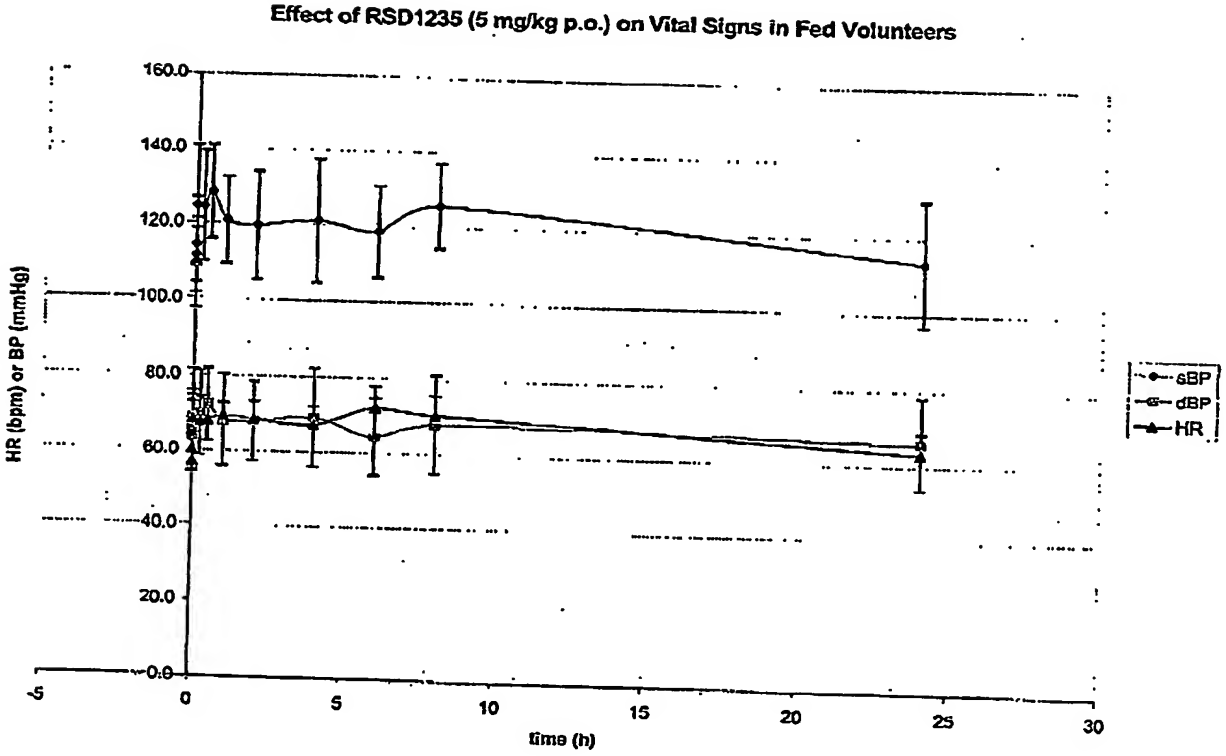

Effect of RSD1235 (5 mg/kg p.o.) on Vital Signs in Fed Volunteers
HR (bpm) or BP (mmHg)
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
-5
0
5
10
15
20
25
30
time (h)
sBP
dBP
HR

Figure 3

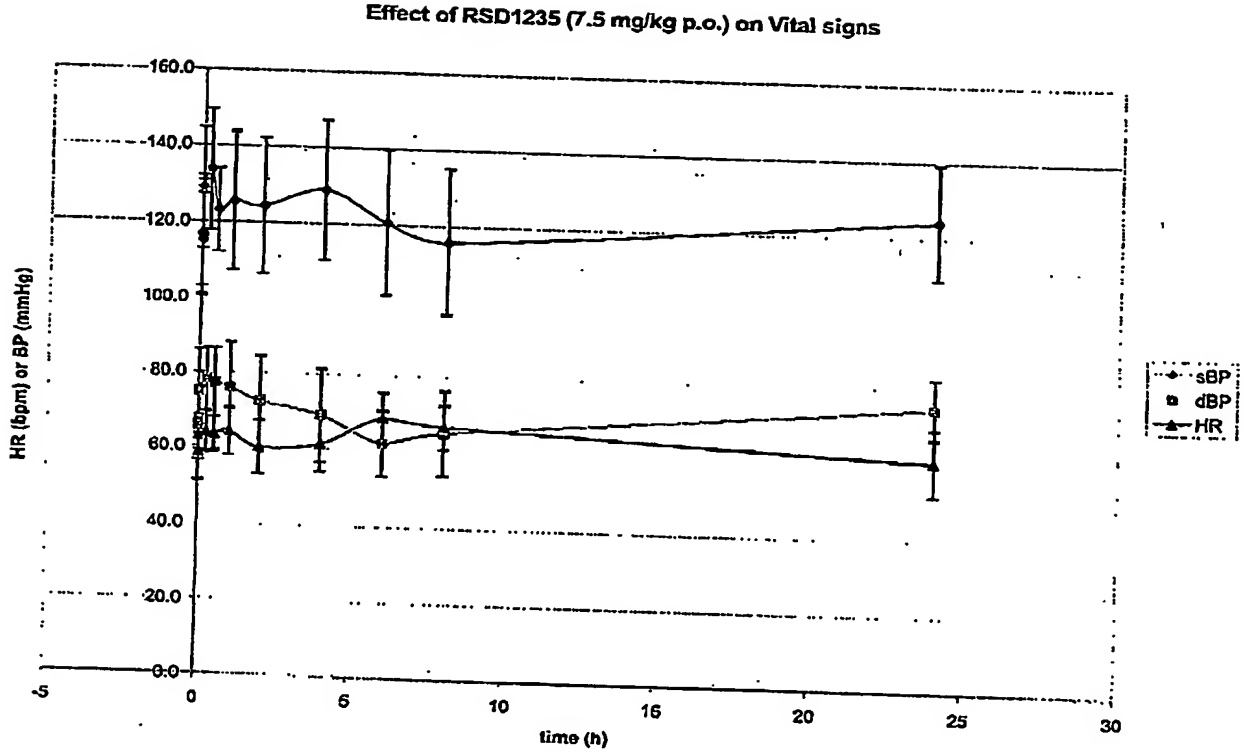

Effect of RSD1235 (7.5 mg/kg p.o.) on Vital signs
HR (bpm) or BP (mmHg)
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
-5
0
5
10
15
20
25
30
time (h)
sBP
dBP
HR

Figure 4: ECG Intervals in "fasted" Volunteers
RSD1235 (5 mg/kg p.o.)

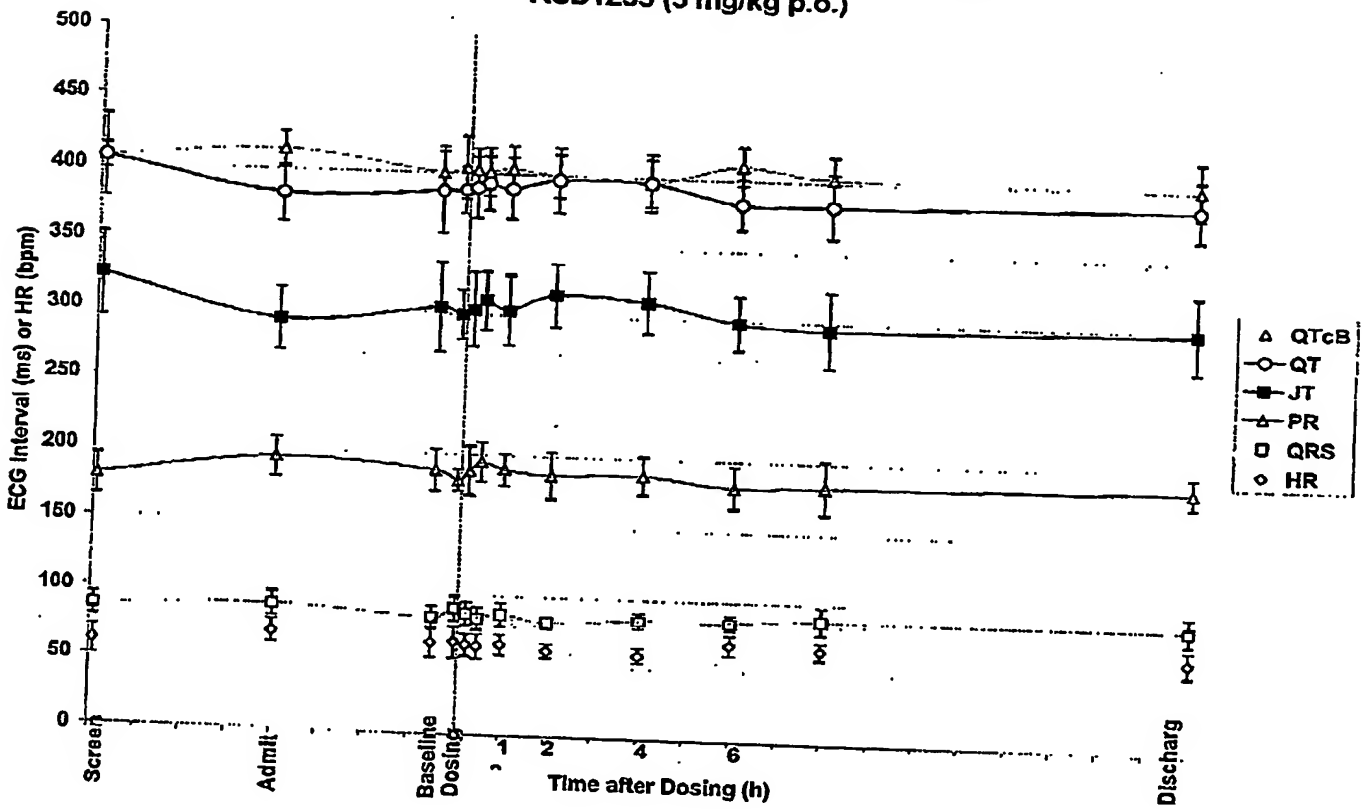


Figure 5: ECG Intervals in "fed" Volunteers
RSD1235 (5 mg/kg p.o.)

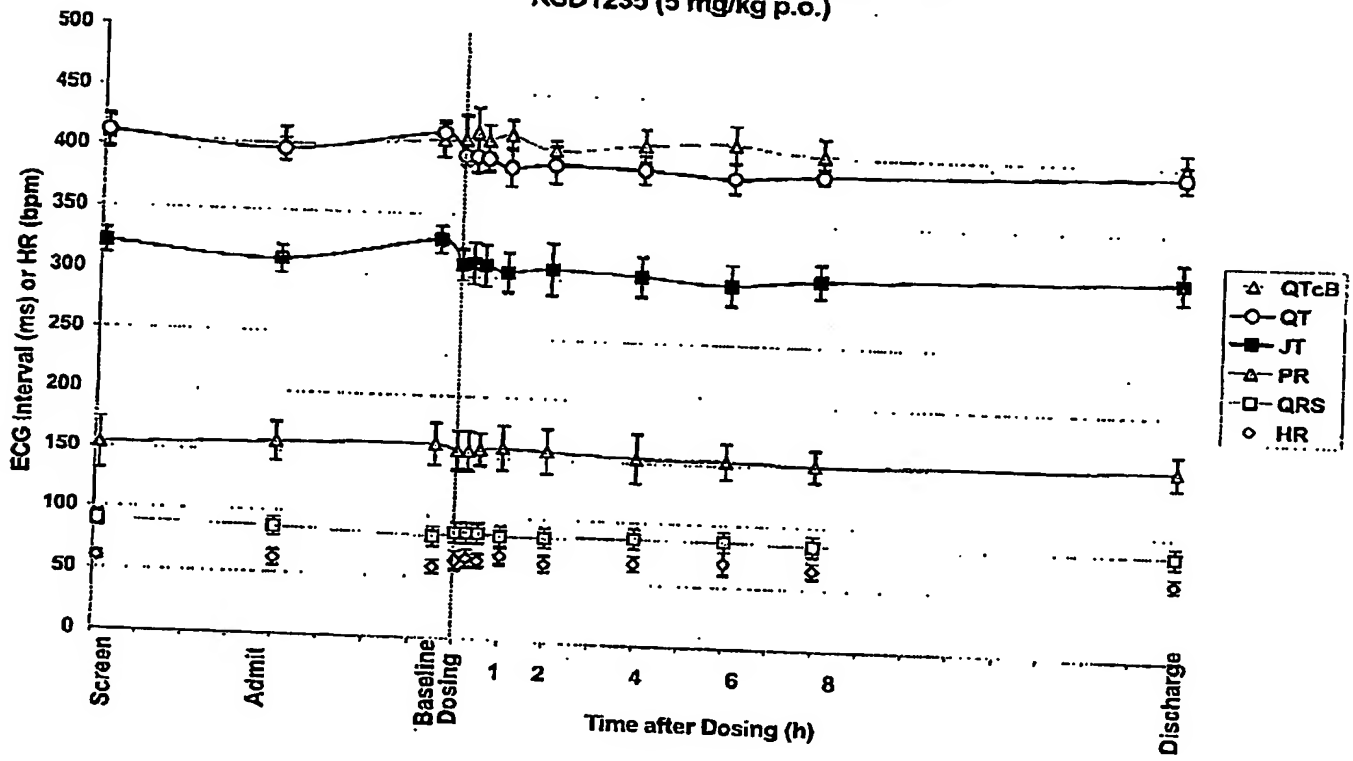


Figure 6: ECG Intervals in "fasted" Volunteers
RSD1235 (7.5 mg/kg p.o.)

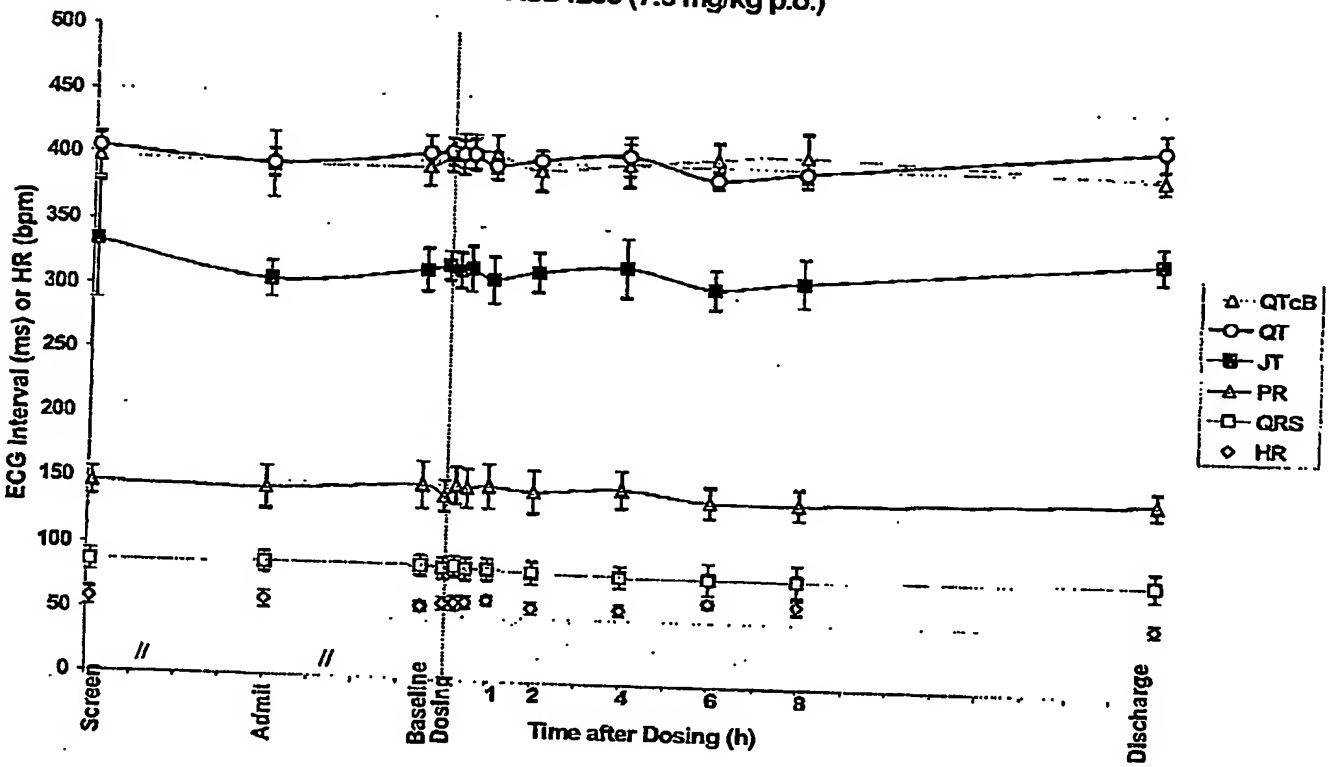
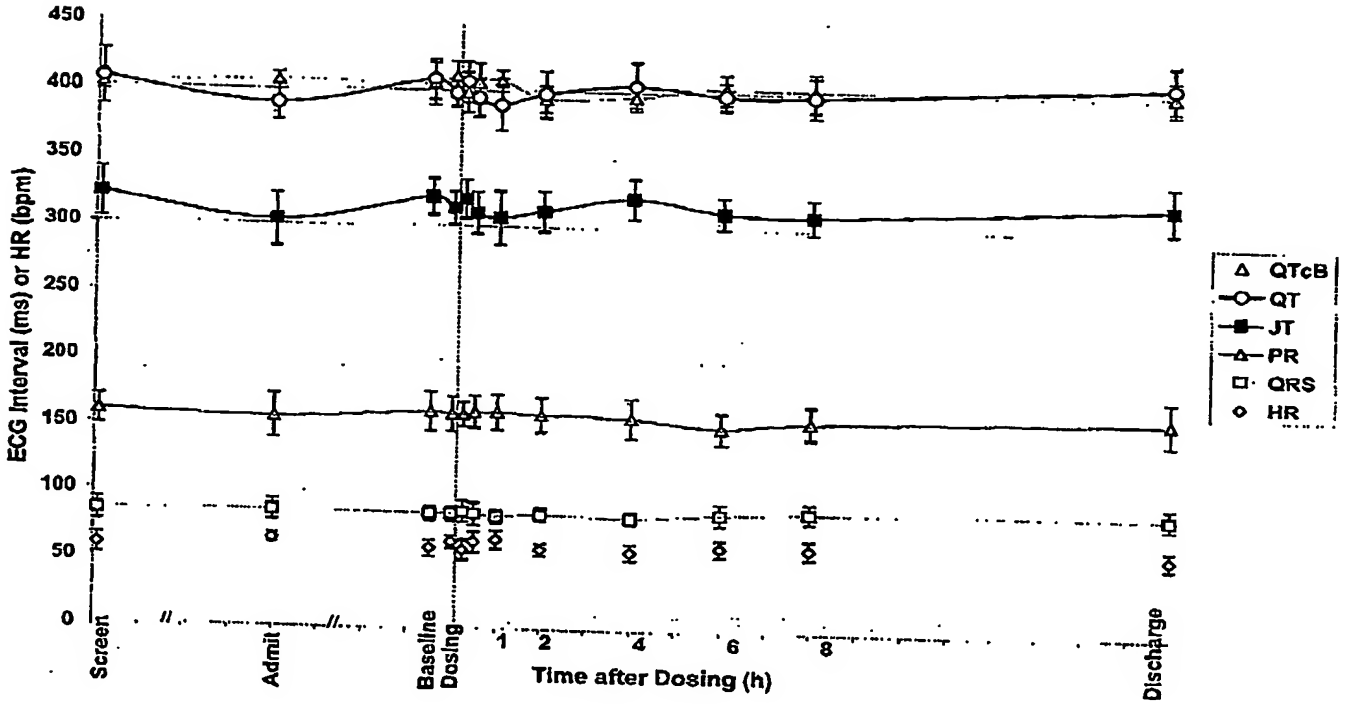


Figure 7. ECG Intervals in Placebo Volunteers



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